Synthesis of 4-(Pyrazol-5-yl)-1,2,4-triazole-3-thiones

Chiara B. Vicentini*, Maurizio Manfrini, Augusto C. Veronese and Mario Guarneri

Dipartimento di Scienze Farmaceutiche, Università degli Studi, 44100 Ferrara, Italy

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Condensation of pyrazolyl isothiocyanates **2** with *N*-substituted hydrazines provided the 2-methyl/phenyl-4-(pyrazol-5-yl)thiosemicarbazides **3**. Cyclization of **3** with formic acid-acetic anhydride or with triethyl orthoacetate-acetic anhydride provided 4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **4a-f** and 5-methyl-4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **4g-l** respectively.

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New changing problems in plant protection technology have promoted research to discover more efficient pesticides. In particular the development of herbicides, now an unavoidable means to selectively control the growth of weeds, resulted in a whole range of azoles exhibiting high levels of activity, application flexibility, crop tolerance and low levels of toxicity to mammals. Pyrazoles and triazoles play an important role among this class of heterocycles. A series of pyrazole and 1,2,4-triazole derivatives [1] have been patented and extensively employed in agriculture.

Continuing our efforts toward azoles pesticides [2], we undertook the synthesis of some 4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **4**, which were considered as interesting lead molecules to be explored as potential herbicides.

The title compounds were prepared using the method previously reported for the synthesis of 4-aryl-1,2,4-triazole-3-thiones [3], with appropriate modifications in order to obtain the target 4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **4** variously substituted in positions 2 and 5 of the triazole ring and in positions 1 and 3 of the pyrazole ring.

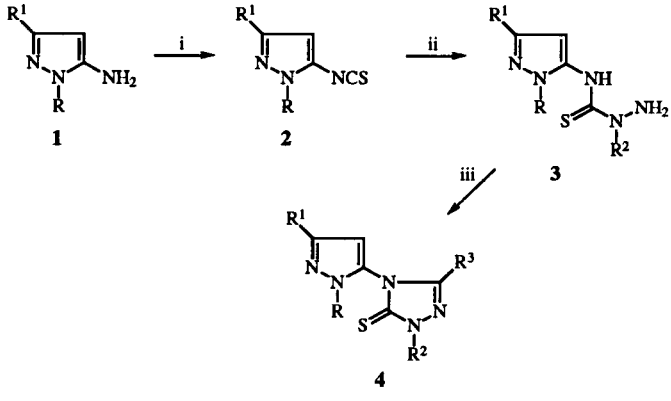
The purpose of the present work was to find a synthetic procedure utilizable to prepare a series of homologues **4** useful for optimization of biological activity.

Treatment of the starting aminopyrazoles **1** with thiophogene in the presence of sodium carbonate afforded the pyrazole isothiocyanates **2**. Condensation of **2** with *N*-substituted hydrazines in ethanol provided the 2-methyl/phenyl-4-(pyrazol-5-yl)thiosemicarbazides **3**. No 1-substituted isomer was detected. The structure of compounds **3** is confirmed by ^{1}H nmr spectroscopy. Two distinct signals attributable to NH_2 and NH are generally detected both in dimethyl sulfoxide-d_6 and in deuteriochloroform solution. While in dimethyl sulfoxide-d_6 the two signals are broad at *ca* 6.00-8.00 ppm and the NH absorption is often under the absorptions of the phenyl hydrogens, in the deuteriochloroform the two absorptions are sharp, and easily attributable (see for instance compound **3e**: NH_2 at 4.53 ppm, NH at 9.30 ppm).

Cyclization of **3** with formic acid-acetic anhydride or with triethyl orthoacetate-acetic anhydride provided 4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **4a-f** and 5-methyl-4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **4g-l**, respectively. The structures of these compounds were confirmed by ^{1}H nmr spectroscopy. Compounds **4a-f** were characterized by two CH absorptions, one in the range 6.17-6.71 ppm (CH of pyrazole ring) and one in the range of 7.53-7.59 (CH of triazole ring). Compounds **4g-l** showed one absorption at 6.13-6.70 ppm (CH of pyrazole ring). All the other signals correspond to the proposed structures.

Biological tests of compounds **4** are in progress.

Scheme



	R	R^1
1a, 2a	Me	Me
1b, 2b	Ph	Me
1c, 2c	Me	Ph

	R	R^1	R^2
3a	Me	Me	Me
3b	Ph	Me	Me
3c	Me	Ph	Me
3d	Me	Me	Ph
3e	Ph	Me	Ph
3f	Me	Ph	Ph

	R	R^1	R^2	R^3
4a	Me	Me	Me	H
4b	Ph	Me	Me	H
4c	Me	Ph	Me	H
4d	Me	Me	Ph	H
4e	Ph	Me	Ph	H
4f	Me	Ph	Ph	H
4g	Me	Me	Me	Me
4h	Ph	Me	Me	Me
4i	Me	Ph	Me	Me
4j	Me	Me	Ph	Me
4k	Ph	Me	Ph	Me
4l	Me	Ph	Ph	Me

Reagents: i, $CSCl_2$; ii, R^2NHNH_2; iii, HCOOH, Ac_2O (R^3 = H) and $MeC(OEt)_3$, Ac_2O (R^3 = Me)

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus. The ir spectra were recorded on a Perkin-Elmer Paragon 500 FT-IR spectrophotometer. The ^{1}H nmr spectra were

recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Column chromatography was performed using Merck silica gel (70-230 mesh); for the flash chromatography technique, silica gel (230-400 mesh) was employed.

General Procedure for the Synthesis of Pyrazolylisothiocyanates **2a-c**.

A solution of pyrazolylamine **1a-c** [4-6] dissolved in 20 ml of dichloromethane was added dropwise to a mixture of 6.34 g (0.06 mole) of sodium carbonate, 12 ml of water and 1.84 ml (0.024 mole) of thiophosgene. After the addition was completed, the suspension was stirred at room temperature for 3 hours; then 10 ml of dichloromethane and 10 ml of water were added, the organic phase was separated, dried (sodium sulfate) and evaporated to yield a residue which was purified by column chromatography.

1,3-Dimethyl-5-isothiocyanatopyrazole (**2a**).

This compound was obtained from **1a** [4] as pale yellow crystals, 1.01 g (54%), mp 160-161° (purified by column chromatography, eluent ethyl acetate:petroleum ether 1:1, v/v); ir (potassium bromide): 2043, 1564, 1488, 1455 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.22 (s, 3H, Me), 3.72 (s, 3H, NMe), 6.01 (s, 1H, CH).

Anal. Calcd. for $C_6H_7N_3S$: C, 47.04; H, 4.61; N, 27.43; S, 20.93. Found: C, 46.93; H, 4.68; N, 27.38; S, 20.88.

5-Isothiocyanato-3-methyl-1-phenylpyrazole (**2b**).

This compound was obtained from **1b** [5] as a colorless oil, 2.02 g (78%) (purified by column chromatography, eluent ethyl acetate:petroleum ether 1:1, v/v); ir (film): 2058, 1594, 1544, 1502 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (s, 3H, Me), 6.20 (s, 1H, CH), 7.35-7.59 (m, 5H, Ph).

Anal. Calcd. for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52; S, 14.89. Found: C, 61.45; H, 4.25; N, 19.43; S, 14.79.

5-Isothiocyanato-1-methyl-3-phenylpyrazole (**2c**).

This compound was obtained from **1c** [6] as pale yellow crystals, 1.76 g (68%), mp 54-56° (purified by column chromatography, eluent ethyl acetate:petroleum ether 3:7, v/v); ir (potassium bromide): 2073, 1533, 1509, 1446 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.84 (s, 3H, Me), 6.51 (s, 1H, CH), 7.20-7.70 (m, 5H, Ph).

Anal. Calcd. for $C_{11}H_9N_3S$: C, 61.37; H, 4.21, N, 19.52; S, 14.89. Found: C, 61.42; H, 4.19; N, 19.48; S, 14.91.

General Procedure for the Synthesis of 2-Methyl/Phenyl-4-(pyrazol-5-yl)thiosemicarbazides **3a-f**.

Methyl or phenylhydrazine (0.01 mole) was added to a solution of 0.01 mole of the pyrazolyl isothiocyanate **2** dissolved in 5 ml of ethanol. After the addition was completed, the reaction mixture was stirred at room temperature for 1 hour and filtered. The product was washed with 1 ml of ice-cold ethanol.

4-(1,3-Dimethylpyrazol-5-yl)-2-methylthiosemicarbazide (**3a**).

This compound was obtained from **2a** and methylhydrazine as colorless crystals, 1.31 g (65%), mp 179-180°; ir (potassium bromide): 3292, 3190, 1634, 1573, 1509 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.08 (s, 3H, Me), 3.49 (s, 3H, NMe), 3.51 (s, 3H, NMe), 5.81 (s, 1H, CH), 6.00-8.00 (br, 3H, NH_2 + NH).

Anal. Calcd. for $C_7H_{13}N_5S$: C, 42.19; H, 6.58; N, 35.14; S, 16.09. Found: C, 42.22; H, 6.55; N, 35.11; S, 16.19.

2-Methyl-4-(3-methyl-1-phenylpyrazol-5-yl)thiosemicarbazide (**3b**).

This compound was obtained from **2b** and methylhydrazine as colorless crystals, 1.96 g (75%), mp 162-163°; ir (potassium bromide): 3258, 1571, 1499 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.21 (s, 3H, Me), 3.46 (s, 3H, NMe), 6.20 (s, 1H, CH), 6.30-7.20 (br, 2H, NH_2), 7.31-7.57 (m, 6H, Ph + NH).

Anal. Calcd. for $C_{12}H_{15}N_5S$: C, 55.15; H, 5.79; N, 26.80; S, 12.27. Found: C, 55.21; H, 5.82; N, 26.75; S, 12.21.

2-Methyl-4-(1-methyl-3-phenylpyrazol-5-yl)thiosemicarbazide (**3c**).

This compound was obtained from **2c** and methylhydrazine as colorless crystals, 2.01 g (77%), mp 191-192°; ir (potassium bromide): 3174, 1566, 1519 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.54 (s, 3H, NMe), 3.64 (s, 3H, NMe), 6.52 (s, 1H, CH), 6.00-7.00 (br, 2H, NH_2), 7.23-7.78 (m, 6H, Ph + NH).

Anal. Calcd. for $C_{12}H_{15}N_5S$: C, 55.15; H, 5.79; N, 26.80; S, 12.27. Found: C, 55.19; H, 5.72; N, 26.85; S, 12.23.

4-(1,3-Dimethylpyrazol-5-yl)-2-phenylthiosemicarbazide (**3d**).

This compound was obtained from **2a** and phenylhydrazine as colorless crystals, 2.33 g (89%), mp 137-138°; ir (potassium bromide): 3263, 1572, 1494 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.10 (s, 3H, Me), 3.57 (s, 3H, NMe), 5.90 (s, 1H, CH), 6.50 (br, 2H, NH_2), 7.24-7.48 (m, 6H, Ph + NH).

Anal. Calcd. for $C_{12}H_{15}N_5S$: C, 55.15; H, 5.79; N, 26.80; S, 12.27. Found: C, 55.22; H, 5.72; N, 26.84; S, 12.23.

4-(3-Methyl-1-phenylpyrazol-5-yl)-2-phenylthiosemicarbazide (**3e**).

This compound was obtained from **2b** and phenylhydrazine as colorless crystals, 2.60 g (80%), mp 190.5-191.5°; ir (potassium bromide): 3220, 3150, 1597, 1569, 1537, 1498 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.31 (s, 3H, Me), 4.53 (s, 2H, NH_2), 6.66 (s, 1H, CH), 7.22-7.52 (m, 10H, 2Ph), 9.30 (br, 1H, NH).

Anal. Calcd. for $C_{17}H_{17}N_5S$: C, 63.13; H, 5.30; N, 21.65; S, 9.91. Found: C, 63.09; H, 5.34; N, 21.71; S, 10.01.

4-(1-Methyl-3-phenylpyrazol-5-yl)-2-phenylthiosemicarbazide (**3f**).

This compound was obtained from **2c** and phenylhydrazine as colorless crystals, 2.06 g (63%), mp 191-193°; ir (potassium bromide): 3294, 3266, 3145, 1562, 1469 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.71 (s, 3H, NMe), 6.62 (s, 1H, CH), 6.90 (br, 2H, NH_2), 7.26-7.60 (m, 11H, 2Ph + NH).

Anal. Calcd. for $C_{17}H_{17}N_5S$: C, 63.13; H, 5.30; N, 21.65; S, 9.91. Found: C, 63.08; H, 5.35; N, 21.57; S, 9.81.

General Procedure for the Synthesis of 2,4-Dihydro-2-methyl/phenyl-4-(pyrazol-5-yl)-3*H*-1,2,4-triazole-3-thiones **4a-f**.

A solution of 2-methyl/phenyl-4-(pyrazol-5-yl)thiosemicarbazide **3** (0.001 mole) in a mixture of 10 ml of formic acid and 2 ml of acetic anhydride was stirred at room temperature for 2 hours; the solvent was evaporated to yield a residue which was purified by column chromatography.

2,4-Dihydro-4-(1,3-dimethylpyrazol-5-yl)-2-methyl-3*H*-1,2,4-triazole-3-thione (**4a**).

This compound was obtained from **3a** as colorless crystals, 179 mg (85%), mp 148-148.5° (purified by flash column chromatography, eluent ethyl acetate:petroleum ether 8:2, v/v); ir

(potassium bromide): 3108, 1565, 1467 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, Me), 3.72 (s, 3H, NMe), 3.85 (s, 3H, NMe), 6.17 (s, 1H, CH), 7.78 (s, 1H, CH).

Anal. Calcd. for $C_8H_{11}N_5S$: C, 45.92; H, 5.30; N, 33.47; S, 15.32. Found: C, 45.88; H, 5.36; N, 33.49; S, 15.36.

2,4-Dihydro-2-methyl-4-(3-methyl-1-phenylpyrazol-5-yl)-3*H*-1,2,4-triazole-3-thione (**4b**).

This compound was obtained from **3b** as colorless crystals, 199 mg (73%), mp 113-114° (purified by column chromatography, eluent ethyl acetate:petroleum ether 8:2, v/v); ir (potassium bromide): 3102, 1542, 1502 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.41 (s, 3H, Me), 3.80 (s, 3H, NMe), 6.48 (s, 1H, CH), 7.37 (s, 5H, Ph), 7.53 (s, 1H, CH).

Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.55; H, 4.83; N, 25.81; S, 11.82. Found: C, 57.58; H, 4.81; N, 25.85; S, 11.85.

2,4-Dihydro-2-methyl-4-(1-methyl-3-phenylpyrazol-5-yl)-3*H*-1,2,4-triazole-3-thione (**4c**).

This compound was obtained from **3c** as colorless crystals, 182 mg (67%), mp 97-99° (purified by column chromatography eluent ethyl acetate:petroleum ether 8:2, v/v); ir (potassium bromide): 3148, 1563, 1492 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.83 (s, 3H, NMe), 3.85 (s, 3H, NMe), 6.65 (s, 1H, CH), 7.37-7.75 (m, 5H, Ph), 7.62 (s, 1H, CH).

Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.55; H, 4.83; N, 25.81; S, 11.82. Found: C, 57.51; H, 4.86; N, 25.77; S, 11.79.

2,4-Dihydro-4-(1,3-dimethylpyrazol-5-yl)-2-phenyl-3*H*-1,2,4-triazole-3-thione (**4d**).

This compound was obtained from **3d** as colorless crystals, 122 mg (45%), mp 188-190° (purified by flash column chromatography, eluent ethyl acetate:petroleum ether 1:1, v/v); ir (potassium bromide): 3127, 1569, 1500 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32 (s, 3H, Me), 3.78 (s, 3H, NMe), 6.24 (s, 1H, CH), 7.41-7.60 (m, 3H, Ph), 7.92 (s, 1H, CH), 8.04-8.08 (m, 2H, Ph).

Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.55; H, 4.83; N, 25.81; S, 11.82. Found: C, 57.49; H, 4.87; N, 25.75; S, 11.73.

2,4-Dihydro-4-(3-methyl-1-phenylpyrazol-5-yl)-2-phenyl-3*H*-1,2,4-triazole-3-thione (**4e**).

This compound was obtained from **3e** as colorless crystals, 170 mg (51%), mp 135-136° (purified by column chromatography, eluent ethyl acetate:petroleum ether 1:1, v/v); ir (potassium bromide): 3120, 1596, 1573, 1498 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.43 (s, 3H, Me), 6.54 (s, 1H, CH), 7.41-7.50 (m, 8H, Ph), 7.69 (s, 1H, CH), 7.97-8.01 (2H, Ph).

Anal. Calcd. for $C_{18}H_{15}N_5S$: C, 64.84; H, 4.53; N, 21.00; S, 9.62. Found: C, 64.75; H, 4.57; N, 20.89; S, 9.57.

2,4-Dihydro-4-(1-methyl-3-phenylpyrazol-5-yl)-2-phenyl-3*H*-1,2,4-triazole-3-thione (**4f**).

This compound was obtained from **3f** as colorless crystals, 160 mg (48%), mp 130-132° (purified by flash column chromatography, eluent ethyl acetate:petroleum ether 2:8, v/v); ir (potassium bromide): 3100, 1565, 1498, 1456 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.67 (s, 3H, NMe), 6.71 (s, 1H, CH), 7.36-7.52 (m, 8H, Ph), 7.95 (s, 1H, CH), 8.08-8.10 (m, 2H, Ph).

Anal. Calcd. for $C_{18}H_{15}N_5S$: C, 64.84; H, 4.53; N, 21.00; S, 9.62. Found: C, 64.79; H, 4.59; N, 20.89; S, 9.58.

General Procedure for the Synthesis of 2,4-Dihydro-5-methyl-2-methyl/phenyl-4-(pyrazol-5-yl)-3*H*-1,2,4-triazole-3-thiones **4g-l**.

A solution of 2-methyl/phenyl-4-(pyrazol-5-yl)thiosemicarbazide **3** (0.001 mole) in a mixture of 2 ml of triethyl ortoacetate and 2 ml of acetic anhydride was heated at reflux for 1 hour; the solvent was evaporated to yield a residue which was purified by column chromatography.

2,4-Dihydro-2,5-dimethyl-4-(1,3-dimethylpyrazol-5-yl)-3*H*-1,2,4-triazole-3-thione (**4g**).

This compound was obtained from **3a** as colorless crystals, 134 mg (60%), 89-90° (purified by flash column chromatography, eluent ethyl acetate:petroleum ether 8:2, v/v); ir (potassium bromide): 1590, 1572, 1447 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.18 (s, 3H, Me), 2.31 (s, 3H, Me), 3.68 (s, 3H, NMe), 3.80 (s, 3H, NMe), 6.13 (s, 1H, CH).

Anal. Calcd. for $C_9H_{13}N_5S$: C, 48.41; H, 5.87; N, 31.36; S, 14.36. Found: C, 48.37; H, 5.93; N, 31.30; S, 14.32.

2,4-Dihydro-2,5-dimethyl-4-(3-methyl-1-phenylpyrazol-5-yl)-3*H*-1,2,4-triazole-3-thione (**4h**).

This compound was obtained from **3b** as colorless oil, 191 mg (67%), (purified by column chromatography, eluent ethyl acetate:petroleum ether 8:2, v/v); ir (film): 1591, 1504 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.88 (s, 3H, Me), 2.42 (s, 3H, Me), 3.77 (s, 3H, NMe), 6.40 (s, 1H, CH), 7.35-7.44 (m, 5H, Ph).

Anal. Calcd. for $C_{14}H_{15}N_5S$: C, 58.93; H, 5.30; N, 24.54; S, 11.23. Found: C, 58.91; H, 5.35; N, 24.49; S, 11.17.

2,4-Dihydro-2,5-dimethyl-4-(1-methyl-3-phenylpyrazol-5-yl)-3*H*-1,2,4-triazole-3-thione (**4i**).

This compound was obtained from **3c** as colorless oil, 200 mg (70%), (purified by column chromatography, eluent ethyl acetate:petroleum ether 8:2, v/v); ir (film): 1589, 1567, 1454 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.22 (3H, Me), 3.60 (s, 3H, NMe), 3.82 (s, 3H, NMe), 6.63 (s, 1H, CH), 7.30-7.50 (m, 3H, Ph), 7.70-7.80 (m, 2H, Ph).

Anal. Calcd. for $C_{14}H_{15}N_5S$: C, 58.93; H, 5.30; N, 24.54; S, 11.23. Found: C, 58.85; H, 5.36; N, 4.47; S, 11.15.

2,4-Dihydro-4-(1,3-dimethylpyrazol-5-yl)-5-methyl-2-phenyl-3*H*-1,2,4-triazole-3-thione (**4j**).

This compound was obtained from **3d** as colorless crystals, 234 mg (82%), mp 94-96° (purified by flash column chromatography, eluent ethyl acetate:petroleum ether 1:1, v/v); ir (potassium bromide): 1599, 1566, 1497 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.26 (s, 3H, Me), 2.34 (s, 3H, Me), 3.74 (s, 3H, NMe), 6.20 (s, 1H, CH), 7.38-7.60 (m, 3H, Ph), 8.00-8.10 (m, 2H, Ph).

Anal. Calcd. for $C_{14}H_{15}N_5S$: C, 58.93; H, 5.30; N, 24.54; S, 11.23. Found: C, 58.85; H, 5.33; N, 24.48; S, 11.18.

2,4-Dihydro-5-methyl-4-(3-methyl-1-phenylpyrazol-5-yl)-2-phenyl-3*H*-1,2,4-triazole-3-thione (**4k**).

This compound was obtained from **3e** as colorless crystals, 292 mg (84%), mp 125-128° (purified by column chromatography, eluent ethyl acetate:petroleum ether 1:1, v/v); ir (potassium bromide): 1595, 1504 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.00 (s, 3H, Me), 2.46 (s, 3H, Me), 6.48 (s, 1H, CH), 7.38-7.57 (m, 8H, Ph), 8.00-8.10 (m, 2H, Ph).

Anal. Calcd. for $C_{19}H_{17}N_5S$: C, 65.68; H, 4.93; N, 20.16; S, 9.23. Found: C, 65.51; H, 4.91; N, 20.18; S, 9.25.

2,4-Dihydro-5-methyl-4-(1-methyl-3-phenylpyrazol-5-yl)-2-phenyl-3*H*-1,2,4-triazole-3-thione (**4l**).

This compound was obtained from **3f** as colorless crystals, 247 mg (71%), mp 133-134.5° (purified by flash column chromatography, eluent ethyl acetate:petroleum ether 1:3, v/v); ir (potassium bromide): 1603, 1561, 1490 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (s, 3H, Me), 3.85 (s, 3H, NMe), 6.70 (s, 1H, CH), 7.36-7.51 (m, 6H, Ph), 7.78-7.84 (m, 2H, Ph), 8.06-8.12 (m, 2H, Ph).

Anal. Calcd. for $C_{19}H_{17}N_5S$: C, 65.68; H, 4.93; N, 20.16; S, 9.23. Found: C, 65.70; H, 4.88; N, 10.13; S, 9.17.

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